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Weis, Nina; Katzenstein, Terese L; Ørbæk, Mathilde; Storgaard, Merete; Pedersen, Gitte; Johansen, Isik S; Moseholm, Ellen

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Nina Weis ,[1,2] Terese L Katzenstein,[3] Mathilde Ørbæk ,[1] Merete Storgaard,[4] Gitte Pedersen,[5] Isik S Johansen,[6] Ellen Moseholm [1]

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[1]Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre, Denmark
[2]Department of Clinical Medicine, Copenhagen University, Copenhagen, Denmark
[3]Department of Infectious Diseases, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[4]Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark
[5]Department of Infectious Diseases, Aalborg University Hospital, Aalborg, Denmark
[6]Department of Infectious Diseases, Odense Universitetshospital, Odense, Denmark

Correspondence to
Dr Nina Weis;
nina.weis@regionh.dk

ABSTRACT

Purpose The purpose of the Danish HIV Birth Cohort (DHBC) is to investigate the significance of HIV-1 infection in pregnancy and after delivery in women living with HIV (WLWH) in Denmark and their children, in the era of antiretroviral therapy and other interventions for treatment and prophylaxis.

Participants All WLWH giving birth to one or more children in Denmark after 31 December 1999 are included, with consecutive ongoing enrolment, if they are living with HIV and pregnant, or if they are diagnosed with HIV in relation to pregnancy, delivery or shortly after delivery.

Findings to date DHBC has been used to describe trends in the management of pregnancies in WLWH and their outcomes on a nationwide basis, mode of delivery and predictors of emergency caesarean section as well as risk factors during pregnancy in WLWH for birth-related complications compared with women from the general population (WGP). We have found that HIV-exposed, but uninfected (HEU) children born to WLWH had a lower median birth weight and gestational age and were at higher risk of intrauterine growth retardation than children born to WGP. We have investigated risk of in-hospital admission and use of antibiotics during the first 4 years of life among HEU children and showed that HEU children had an increased risk of overall hospital admission compared with a matched control group of unexposed children. Further, we compared anthropometric outcomes in children with a matched control group of children not exposed to HIV.

Future plans To continuously investigate the significance of HIV infection and antiretroviral therapy in pregnancy and after delivery in WLWH in Denmark and their HEU children and compare these findings with children born to WGP.

Strengths and limitations of this study

- The Danish HIV Birth Cohort (DHBC) is based on a nationwide, population-based, prospective design including all women living with HIV (WLWH) who give birth in Denmark and their children.
- Use of the unique personal identification number assigned to all Danes allows us to extract data for both the WLWH and their children in national registries.
- Use of national registries ensures prospective, uniformly and neutral data collected on an individual level, restricting the methodological problems of loss to follow-up, selection bias and emigration.
- Linkage to the registries allows identification of a population of controls who are matched on relevant variables.
- The main limitation of the DHBC is the relatively small number of children born to WLWH in Denmark. The DHBC is thus most useful for studies with frequently occurring outcomes.

INTRODUCTION

The management of pregnant women living with HIV (WLWH) has evolved significantly, since the introduction of antiretroviral therapy (ART) for the prevention of perinatal transmission of HIV from mother to child.[1 2] Current recommendations include universal testing of pregnant women for HIV infection, immediate initiation of treatment with a combination of two or more antiretroviral drugs from at least two drug classes (combination ART (cART)), the use of caesarean delivery, if the mother has detectable viral load (VL), avoidance of breast feeding when feasible and post-exposure prophylaxis ART to the child.[3–6] As cART is now recommended and implemented globally to all people living with HIV, an increasing number of WLWH will either conceive or initiate cART during pregnancy, resulting in a growing population of HIV-exposed, but uninfected (HEU) children[7] with exposures to HIV and cART in utero which in early life may have potential long-term adverse effects in the children.[8]

The Danish population consists of 5.7 million inhabitants with an estimated adult HIV prevalence of 0.1%.[9 10] There are approximately 1600 WLWH in Denmark, of whom 80% are of childbearing age.[11 12] The majority of WLWH in Denmark are immigrants, mainly from sub-Saharan Africa, and primarily infected with HIV by sexual contact.[13] We have formerly shown that the majority of WLWH in Denmark have few HIV-related symptoms, are sexually active and have a strong desire for children.[14] The healthcare system in Denmark is tax-based and ensures universal access to both medical healthcare and many social support services.[15] Hence, ART is provided free of charge and people

Table 1 Data collected in the Danish HIV Birth Cohort

Domain	Variable
Maternal demographics	Name
	Date of birth
	Country of birth
	Body mass index prior to pregnancy
	HIV positive date
	Time of diagnosis in relation to pregnancy
	Transmission route
Maternal medical history	Hepatitis B and/or C infection
	Comorbidity
	AIDS diagnosis
	CD4 count at diagnosis
	HIV RNA at diagnosis
	Smoking
	Alcohol use
	Drug use
Family history	Paternal HIV status
	Other children
ART treatment	ART treatment prior to pregnancy
	Initiation of treatment
	Change in treatment during pregnancy
	Retrovir during labour
	Continuation of ART after delivery
	Other medications during pregnancy
Pregnancy and delivery	Estimated date of delivery
	Planned pregnancy
	Fertility help
	Conception
	Birth plan
	CD4 count in early pregnancy
	HIV RNA in early pregnancy
	Vitamin D in pregnancy
	Multiple/single birth
	Intrauterine growth
	Bleeding during pregnancy
	Amniocentesis
	Placenta biopsy
	Folic acid treatment
	CD4 count prior to delivery
	HIV RNA prior to delivery
	Mode of delivery
	Complications
	Pre-eclampsia
	Vacuum-assistance
	Scalp lead placement
	Baby heart rate during delivery
	Artificial rupture of membranes
	pH umbilical cord
Child	Date of birth
	Sex
	Birth weight
	Birth length
	Head circumference
	Apgar score
	Gestational age
	Anaemia at birth
	First objective clinical examination
	ART given to the child
	Other medications
	Breast feeding
	First HIV PCR result
	HIV status at 3, 6 and 18 months
	Transmission of HIV
	Objective clinical examination at 18 months

ART, antiretroviral therapy.

living with HIV in Denmark are generally well treated (VL <50 copies/mL) with life expectancies approaching those of the general population.[16] National antenatal screening for all pregnant women has been implemented as an opt-out programme (eg, all women are screened unless they decline).[17] The proportion of WLWH that are diagnosed during pregnancy range between 18%–37%.[13 18] Treatment with cART has been recommended to all pregnant WLWH in Denmark since the late 1990s and most women have an undetectable VL at the time of delivery, resulting in a decreased risk of perinatal transmission to <1%.[13 19] Condom-less sex (without support from artificial reproductive technologies) and vaginal delivery are recommended in well-treated WLWH.[19 20] New-born treatment with prophylactic antiretroviral medicine lasts for 4 weeks after birth.[21 22]

Children born to WLWH with a HIV RNA <50 copies/mL are treated with zidovudine for 4 weeks while children born to WLWH with a HIV RNA >50 copies/mL are treated with zidovudine, lamivudine and nevirapine for a minimum of 4 weeks.

The Danish HIV Birth Cohort (DHBC) is a nationwide, prospective cohort, set up to monitor the significance of HIV in pregnancy and its outcome in children born to WLWH in Denmark. The cohort was set up by a scientific management team consisting of clinicians and

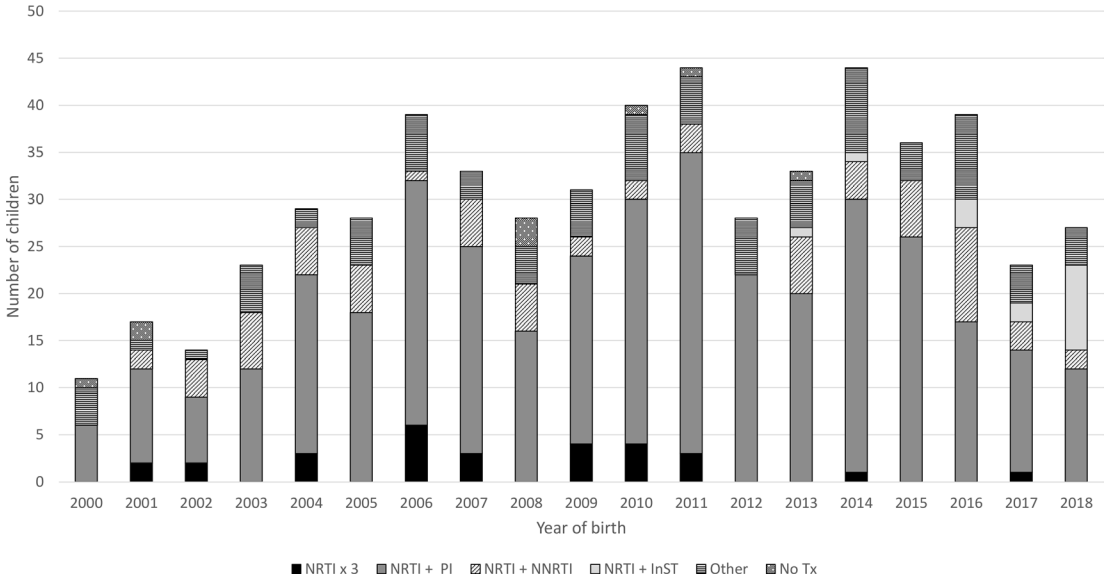

Figure 1 Number of 569 children born to 402 women living with HIV in Denmark and included in the Danish HIV Birth Cohort by year of birth and maternal treatment at delivery. InST, integrase strand transfer inhibitors; NRTI; nuklos(t)ide reverse transcriptase inhibitors; NNRTI, non-nuklos(t)ide reverse transcriptase inhibitors; PI, protease inhibitors; Tx: treatment.

researchers from the five clinical departments of infectious diseases treating pregnant WLWH in Denmark. All five departments are located at University Hospitals in four of the five regions in Denmark. Both treatment of HIV as well as prepartum and postpartum care are done in accordance with national guidelines.

The cohort is located at Copenhagen University Hospital—Hvidovre, Copenhagen, Denmark. The overall aim of the DHBC is to investigate the significance of HIV infection in pregnancy and after delivery in WLWH in Denmark and their children, in the era of antiretroviral therapy and other interventions for treatment and prophylaxis.

The DHBC is approved by the Danish Data Protection Agency (2012-58-0004; AHH-2017–027), the Danish Medical Agency (3-3013-406/4) and Center for Regional Development, Capital Region (R-20049159) as a clinical research database with data registry in a Research Electronic Data Capture (REDCap) system. Individual consent for collection of data for research purposes is provided from all women included in the DHBC. According to Danish Law, approval from the National Committee on Health Research Ethics is not required as no biomedical intervention is performed. The national registries and Statistics Denmark are administered by national authorities.

COHORT DESCRIPTION

The DHBC is a prospective, nationwide, population-based cohort study including all WLWH giving birth to one or more children in Denmark after 31 December 1999, with consecutive ongoing enrolment. Women are included if they are living with HIV and pregnant, or if they are diagnosed with HIV in relation to pregnancy, delivery or shortly after delivery. Women who are diagnosed with HIV at a later time point after giving birth, when time of transmission cannot be determined to be prior to or during pregnancy are excluded. Information about miscarriages or stillbirths in WLWH are not included in the cohort. Eligible women are identified and enrolled in the DHBC through the clinical departments by the clinicians responsible for the treatment and management of pregnant WLWH. Hence, the risk that a woman is missed in the DHBC is negligible. The DHBC collects clinical and demographic data on both the mother and the child from the medical records and all data are entered prospectively into a REDCap database. Baseline data are collected the year the child was born. Annual updates are performed.

Baseline data are collected the year the child is born, including maternal demographics, maternal medical history, family history, cART treatment, pregnancy and delivery and among others on the children's date of birth, sex, birth length and birth weight, head circumference, Apgar score, gestational age, ART, other medications, breast feeding and HIV transmission (table 1).

The DHBC includes 569 children born in year 2000–2018 to 402 WLWH, including seven pairs of twins. The number of children born to WLWH have increased over time (figure 1). The demographics of the cohort are presented in table 2. The pregnancy was planned in a little more than half the women (58%, n=330), and in 153 pregnancies (46%) it was planned together with an infectious disease specialist. One hundred and three (18%) were diagnosed with HIV during pregnancy, and nine women were diagnosed during birth or shortly afterwards. Information about coinfection with hepatitis B and C were not available for all WLWH included in DHBC, but of the 402 WLWH, 28 (5%) were hepatitis B surface Antigen (HBsAg) positive and 129 (23%) had anti-HBs

Table 2 Baseline characteristics

	Total n=569
Maternal characteristics	
Maternal age at birth (mean (95% CI))*	32.9 (32.4 to 33.4)
Missing	5
Country of origin (n (%))	
Danish	130 (23)
African	327 (58)
Asian	65 (11)
Other	47 (8)
Comorbidity (n (%))	144 (25)
Unknown	35 (6)
Smoking (n (%))	
During pregnancy	67 (12)
Former smoker	28 (5)
Missing	46 (8)
Nulliparous (n (%))	209 (37)
Time of maternal HIV diagnosis (n (%))	
Prior to pregnancy	457 (80)
During pregnancy	103 (18)
During/after delivery	9 (2)
Duration from diagnosis of HIV to delivery (years) (n (%))	5 (1–9)
Mode of HIV transmission (n (%))	
Sexual	372 (65)
Injection drug use	17 (3)
Other/missing	180 (32)
Antiretroviral therapy treatment at delivery (n (%))	
Three NRTIs	29 (5)
Two NRTIs+NNRTI	71 (12)
Two NRTIs+PI	356 (62)
Two NRTIs+InST	18 (3)
Other	89 (16)
No treatment prior to delivery	9 (2)
Intrapartum prophylaxis (n (%))	246 (43)
No intrapartum prophylaxis	275 (49)
Missing	48 (8)
CD4 cell count at delivery (n (%))	
>500 cells/µL	268 (47)
200–499 cells/µL	237 (42)
<200 cells/µL	25 (7)
Missing	39 (7)
HIV viral load at delivery (n, %)	
<50 copies/mL	479 (84)
≥50 copies/mL	62 (11)
Missing	28 (5)
Child characteristics†	
Year of birth (n (%))	
2000–2006	161 (28)
2007–2008	61 (11)
2009–2016	345 (61)
Gestational age <37 weeks (n (%))	52 (9)
Missing	97 (17)
Mode of delivery (n (%))	
Vaginal delivery	211 (37)
Planned caesarean section	218 (38)
Acute caesarean section	128 (23)
Missing	12 (2)
Birth weight, g (mean (95% CI))	3140.7 (3082.7 to 3197.3)
Missing	40 (7)
Birth length, cm (mean (95%)	49.9 (49.7 to 50.3)
Missing	75 (13)
Child sex (n (%))	
Boy	275 (48)
Girl	261 (46)
Missing	33 (6)
Apgar score at 10 min <7 (n (%))	8 (1)
Missing	23 (4)

*Number of HIV-exposed uninfected children born to 402 women living with HIV (WLWH).
†Children born to WLWH with HIV RNA <50 copies/mL are treated with zidovudine for 4 weeks while children born to WLWH with HIV RNA >50 copies/mL are treated with zidovudine, lamivudine and nevirapine for a minimum of 4 weeks.
InST, integrase strand transfer inhibitors; NNRTI, non-nuklos(t)ide reverse transcriptase inhibitors; NRTI, nuklos(t)ide reverse transcriptase inhibitors; PI, protease inhibitors; Tx, treatment.

while 14 (2%) were hepatitis C virus (HCV-RNA) positive and 22 (4%) were anti-HCV positive.

Most WLWH were on cART at delivery, with the majority having undetectable VL at the time of delivery. The median gestational age was 39 weeks (IQR 38–40, range 24–40 weeks). Definitive exclusion of HIV infection of the children is based on two negative virological test results prior to or at 18 months of age. Perinatal transmission of HIV occurred in four children. In all these cases, the mother was diagnosed just prior to, during or shortly after delivery, and none of the four women received cART prior to delivery.

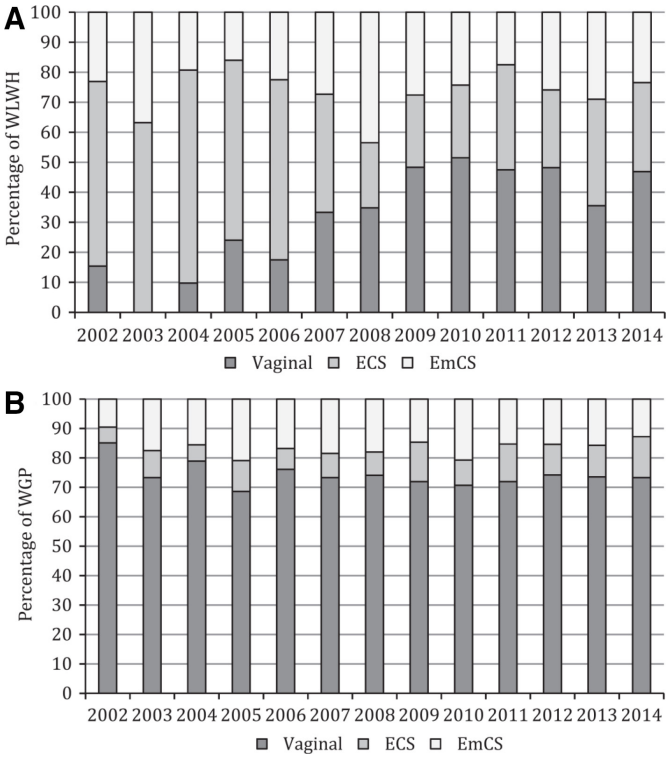

Figure 2 Changes in mode of delivery during 2002–2014 in (A) women living with HIV (WLWH) and (B) women in the general population (WGP)[13] ECS, elective caesarean section; EmCS, emergency caesarean section.

Using the unique 10-digit personal identification number (PIN), assigned to all Danish residents at birth (or with approved immigration status), the DHBC is linked to the national registries and data from Statistics Denmark containing medical and sociodemographic information on the whole Danish population.[23–25] This data linkage allows us to capture comparison cohorts, as well as ascertain immigration, emigration and death.[23]

The DHBC has been linked to the following registries: the Medical Birth Registry, which contains complete information on all births in Denmark since 1973[26]; the National Patient Registry, which contains information on all inpatient and outpatient hospital admissions in Denmark since 1977[27]; the Danish National Prescription Registry, established in 1994 which contains information on all redeemed prescriptions dispensed in Danish Community Pharmacies on an individual level[28]; the Children's Database, which contains all height and weight measurements recorded by medical doctors and nurses during the annual preventive health checks offered to all Danish children until school year 7,[29] and the sociodemographic registries at Statistics Denmark. Data from the national registries and Statistics Denmark are anonymised and accessed through a remote connection to a server at Statistics Denmark.[25]

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Findings to date

In 2010 DHBC data were used to describe trends in the management of pregnancies in WLWH and their outcomes on a national basis.[19] The annual number of HIV pregnancies increased significantly during the study period and substantial changes in pregnancy management were seen. No perinatal transmissions occurred in WLWH, who received treatment according to the national guidelines at that time, that is, cART before week 22, intravenous zidovudine (ZDV) during labour, neonatal ZDV for 4–6 weeks and no breastfeeding.[19]

Mode of delivery and predictors of emergency caesarean section (EmCS) in WLWH compared with women from the general population (WGP) was assessed in a paper by Ørbæk *et al*.[13] The number of WLWH who had a vaginal delivery increased over time, especially after the change in guidelines in 2007 offering vaginal delivery to WLWH with suppressed VLs. Compared with WGP more WLWH planned and delivered by planned caesarean section and they had a twofold higher risk of EmCS (figure 2). EmCS was predicted by age >40, African country of origin, asphyxia, delivery during the evening/night, preterm delivery and premature rupture of the membranes (PROM).[13] A recent study showed that WLWH had more risk factors during pregnancy, including high body mass index (>25), smoking, prior perinatal deaths, prior caesarean section, viral hepatitis (chronic hepatitis B and C) and psychiatric disorders (DO993B1-5) and a higher risk of postpartum haemorrhage and EmCS than WGP.[30] The risk of most birth-related complications was similar between the groups. Children born to WLWH had a lower median birth weight and gestational age and were at higher risk of intrauterine growth retardation.[30]

It has been suggested that exposures to HIV and cART in utero may have adverse effects on infant development and growth.[31–33] Using DHBC data, we compared anthropometric outcomes in HEU children with a matched control group of children not exposed to HIV.[34] HEU children were smaller (defined as weight-for-age *z-score*) and shorter (defined as length-for-age *z-score*) at birth, but this difference decreased with time and there was no significant difference between the groups at >18 months of age (figure 3). As the z-score already controls for age, gestational age (for children born <37 weeks gestation) and sex, these factors were not further controlled for. The absolute difference in weight and length between HEU and the control group children were relatively small, and was not considered to have a negative effect on the health and well-being of HEU children in early childhood.[34]

It has also been hypothesised that exposure to HIV and/or cART in utero or in the postnatal period may affect the development of the infant's immune and other organ systems, resulting in higher morbidity rates among HEU compared with unexposed children.[35–38] Our study investigating risk of in-hospital admission and use of antibiotics during the first 4 years of life among HEU children, showed that HEU children had an increased risk of overall hospital admission compared with a matched

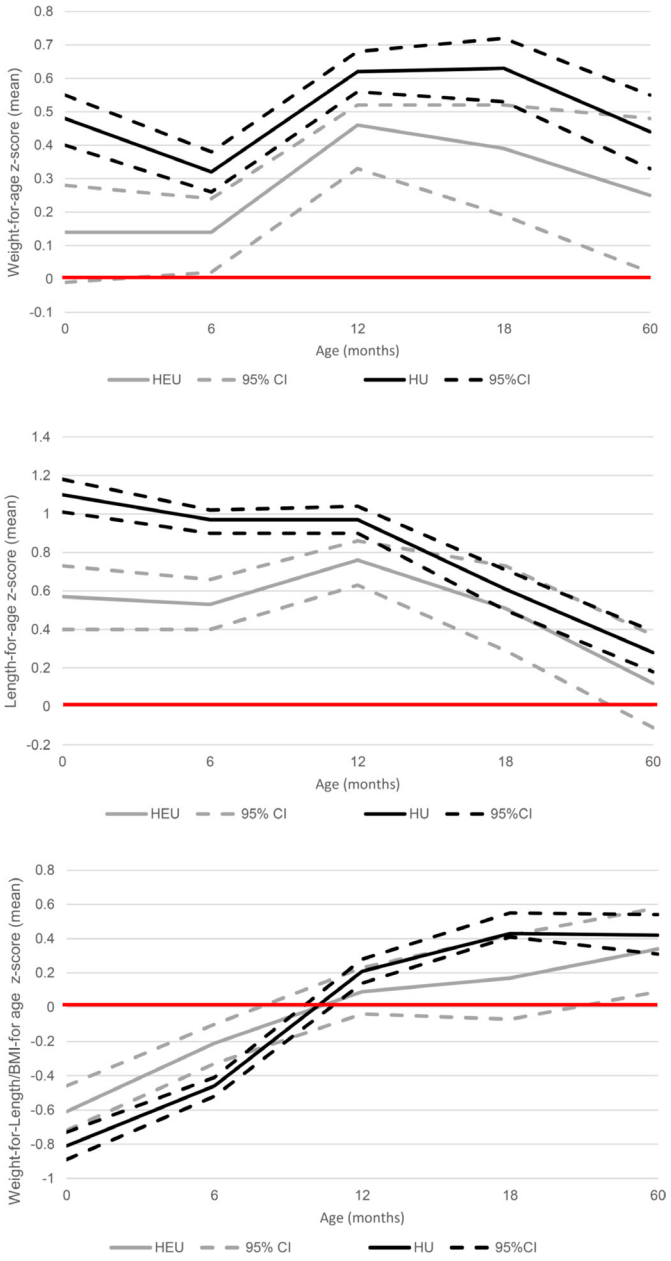

Figure 3 Predicted effect over time of WAZ, LAZ and WLZ/BMIz z-scores from birth until the age of 5 years from the mixed regression models.[34] BMI, body mass index; HEU, HIV-exposed, but uninfected; HU, HIV-unexposed; LAZ, length-for-age; WAZ, weight-for-age; WLZ, weight- for-lenght.

control group of unexposed children. This was mainly due to an increased risk of admission due to observation/non-specific diagnosis, and there was no increased risk of admission due to infectious disease.[39] Thus, the excess risk of admission among HEU children may be related to prophylactic treatment and/or HIV testing of the infant rather than somatic disease related to HIV and/or cART exposure.[39]

Strengths and limitations

The main strengths of the DHBC is the nationwide, population-based, prospective design including all WLWH who give birth in Denmark. Use of the unique PIN assigned to all Danes allows us to extract data for both the WLWH and their children in national registries. The use of registries ensures prospective, uniformly and neutral data collected on an individual level, restricting the methodological problems of loss to follow-up, selection bias and emigration. Moreover, linkage to the registries allow us to identify a population of controls who are matched on relevant variables. The main limitation of the DHBC is the relatively small number of children born to WLWH in Denmark. The DHBC is thus most useful for studies with frequently occurring outcomes.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Potential collaborators are welcome to contact the study director Nina Weis (nina.weis@regionh.dk). Data from the Danish HIV Birth Cohort (DHBC) can be shared with researchers with projects that fall within the overall aim of the DHBC which is to investigate the significance of HIV infection in pregnancy and after delivery in women living with HIV and their children after approval is obtained from the Danish Protection Agency (https://datatilsynet.dk). We encourage collaboration with researchers working with similar data.

ORCID iDs
Nina Weis http://orcid.org/0000-0002-3133-2724
Mathilde Ørbæk http://orcid.org/0000-0003-0737-8076
Ellen Moseholm http://orcid.org/0000-0002-7195-8641

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